8EHQ-0704-14915

MR 27694/

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July 2, 2004

Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, D.C. 20460

8EHQ-01-14915

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Dear 8(e) Coordinator:

8EHQ-01-14915
Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, ether with
α-fluoro-ω-(2-hydroxyethyl)poly(difluoromethylene) (1:1)

This letter is to inform you of the results of a follow-up reproduction study conducted in rats with the above referenced test substance. In the initial 90-day toxicity and one-generation reproduction study reported to the Agency, (August 10, 2001 and November 5, 2001), rats were dosed by gavage at doses of 25 mg/kg/day and above. At that time we reported a reduced fertility index and increased estrus cycle length at all dose levels. The estrus cycle lengths were within historical control ranges, but a no-observed-adverse effect level (NOEL) for reproduction was not determined, based on the finding of decreased fertility. This follow-up study was conducted to determine the repeatability of the fertility and estrus cycle effects and to establish a NOEL for this test substance.

A one-generation follow-up reproduction study was conducted with the test substance. Crl:CD®(SD)IGS BR rats (24/sex/dose level) were dosed with the test substance once daily by gavage at dose levels of 0, 1, 10, or 25 mg/kg/day. Following 70 days of dosing (premating), the P1 generation males and females were cohoused within their respective treatment groups, to produce F1 litters. Dams were allowed to deliver and rear their offspring until postpartum day 4. Clinical observations, body weight, and food consumption were determined at least weekly throughout the study. Litter examinations (pup viability, individual pup weights, clinical observations) were determined at birth and on day 4 of the lactation period. Estrus cycle parameters (percent days in diestrus, proestrus, and estrus) and estrus cycle length were evaluated for 3 weeks prior to and during cohabitation in P1 rats.

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After litter production, all P1 rats were given a gross pathological examination, the liver was weighed, and the liver and reproductive organs were preserved for possible microscopic examination. Target organs (liver) and gross lesions from all P1 rats in the control and 25 mg/kg/day groups were examined microscopically; tissues in the low and intermediate groups were subsequently evaluated as needed to determine a no-adverse-effect level. Reproductive organs from P1 rats with suspected reduced fertility were examined microscopically.

The only test substance-related effect observed in this study was increased liver weight in P1 male and female rats, a finding that was not considered adverse. There were no gross or microscopic observations in the liver at 25 mg/kg/day, or in the reproductive organs of P1 males and females that did not produce litters. There were no effects of treatment on other parameters at any dosage: mortality, clinical observations, body weight and food consumption, precoital interval, mating and fertility indices, gestation length, number of implantation sites and corpora lutea, and implantation efficiency. In F1 litters, the number of pups (born, born alive, alive on day 4), sex ratio, viability during lactation days 0-4, and clinical observations were comparable across groups.

In this study, the fertility index was similar across groups (Table 1), as was the mean length of the estrus cycle (Table 2). This differs from the previous study, in which the fertility index at all dose levels was lower than in the control group (Table 1), and the length of the estrus cycle was increased (Table 2).

Table 1. Fertility Index in Rats Dosed with Test Substance

	Dose (mg/kg/day)					
	0	1	10	25	100	500
1st Study	85	-	-	55	58	65
2nd Study	92	88	91	100	-	-

$$\text{Fertility Index} = \frac{\text{Number of pregnant females}}{\text{Number of females that mated}} \times 100$$

Table 2. Estrus Cycle Length in Rats Dosed with Test Substance

	Dose (mg/kg/day)					
	0	1	10	25	100	500
1st Study	4.3	-	-	4.7	4.9	4.8
2nd Study	4.7	4.5	4.4	4.1	-	-

The differing results for estrus cycle length can be easily attributable to normal variability in this parameter since values in both studies were within the testing laboratory's historical control range (4.1-4.9; 14 studies from 1999-2003). Although fertility indices of 55-65% in the first study are outside the testing laboratory's historical control range (72-100%; 10 studies from 1999-2003), it is likely to have been incidental for the following reasons: 1) the low fertility in the first study was similar at all dose levels and thus, was not dose-related; 2) there were no other corroborative findings of reproductive toxicity in the first study that would be predictive of low fertility; 3) the low fertility observed in the first study at 25 mg/kg/day (55%) was not reproduced in the second study, where it was 100%.

Under the conditions of this study, the no-observed-adverse-effect level (NOEL) for P1 rats, F1 offspring, and reproductive parameters, including fertility, was 25 mg/kg/day, the highest dose tested. The apparent increase in estrus cycle length and the decreased fertility reported in the original letter are unlikely to be test substance related.

Sincerely,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.

Director – Regulatory Affairs and Occupational Health

AMK/EM/JCS:clp

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